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RELATIONSHIP OF DOSE RATE AND TOTAL DOSE TO RESPONSES OF CONTINUOUSLY IRRADIATED BEAGLES*

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Abstract

RELATIONSHIP OF DOSE RATE AND TOTAL DOSE TO RESPONSES OF CONTINUOUSLY IRRADIATED BEAGLES

Young-adult beagles were exposed continuously (22 hours/day) to ^{60}Co γ-rays in a specially constructed facility. The exposure rates were either 5, 10, 17, or 35 R/day, and the exposures were terminated at either 600, 1400, 2000, or 4000 R. A total of 354 dogs were irradiated; 221 are still alive as long-term survivors, some after more than 2000 days.

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The data on survival of these dogs, coupled with data from similar preliminary experiments, allow an estimate of the LD_{50} for γ-ray exposures given at a number of exposure rates. They also allow comparison of the relative importance of dose rate and total dose, and the interaction of these two variables, in the early and late effects after protracted irradiation. The LD_{50} for the beagle increases from 258 rad delivered at 15 R/minute to ∿3000 rad at 10 R/day. Over this entire range, the LD_{50} is dependent upon hematopoietic damage. At 5 R/day and less, no meaningful LD_{50} can be determined; there is nearly normal continued hematopoietic function, survival is prolonged, and the dogs manifest varied individual responses in other organ systems.

Although the experiment is not complete, interim data allow several important conclusions. Terminated exposures, while not as effective as radiation continued until death, can produce myelogenous leukemia at the same exposure rate, 10 R/day. More importantly, at the same total accumulated dose, lower exposure rates are more damaging than higher rates on the basis of the rate and degree of hematological recovery that occurs after termination of irradiation. Thus, the rate of hematologic depression, the nadir of the depression, and the rate of recovery are dependent upon exposure rate; the latter is inversely related and the former two are directly related to exposure rate.

INTRODUCTION

Studies of protracted irradiation have largely focused on the results of irradiation given until death and many have used intermittent and not continuous exposures [1-6]. Mammals given whole-body irradiation from high energy γ-ray sources develop symptoms and lesions and have associated survival times that are highly dependent upon both total dose and dose rate [1-7]. Exposure rates in excess of 5 R/minute produce symptomatology that is determined primarily by total dose. At these

high exposure rates, a few hundred rads is a midlethal or LD_{50} dose and death results within a few days to a few weeks [8]. Changes of a few rads, more or less, determine the death of recovery of the animal. Our own studies with dogs irradiated continuously to death have shown that exposure rates above 5 R/day result in deaths that are related solely to damage to the hematopoietic system [9,10]. Although different immediate causes of death occur, the basic damage is to the orderly production of the cellular elements of the blood. Differential damage to production and maturation of granulocytes and erythrocytes leads to death from septicemia and anemia, respectively. At exposure rates of 5-10 R/day, there is early suppression of peripheral blood values, but in ~ 50% of exposed animals there is recovery toward normal values indicating an accommodation to the radiotoxic affects. This recovery or accommodation phenomenon leads eventually to hyperplasia of the granulocytes and ultimately to death from leukemia. This syndrome, hematopoietic perturbation leading to leukemia, will be discussed in another paper at this symposium [11].

When whole-body irradiation is continued until death, the causes of death are highly correlated with dose rate, and bone marrow is the critical tissue. However, when the irradiation is terminated at predetermined levels of total exposure, the results are quite different. The animals can recover from or escape the acute hematological effects, and the relative importance of dose and dose rate is less well known[7,12,13]. Further, although the life shortening aspects of continuous irradiation (time to death and dose rate effects) have been evaluated at this Laboratory and by other workers, the physiological, clinical, organ and tissue responses have received less critical evaluation, particularly in long-lived animals [1,14,15].

This report will summarize interim data from an ongoing study of the late effects of predetermined total exposures of whole-body ^{60}Co γ irradiation given to beagle dogs at several different daily dose rates. The objective is to determine whether or not the late effects produced by a given total dose of irradiation are significantly influenced by dose rate.

MATERIALS AND METHODS

A description of the closed beagle colony at Argonne and its management have been published previously [16].

Groups of young adult beagles of both sexes (~ 400 day old) were exposed 22 hours/day at four different exposure rates to predetermined total exposures of ^{60}Co γ-rays in a specially constructed facility [7]. Total exposures of 600 and 1400 R were given at 35, 17, 10, and 5 R/day; 200 R was given at 17, 10, or 5 R/day; 4000 R at 10 and 17 R/day. Enough dogs were irradiated in each of the above groups to produce approximately 20 dogs that survived more than 100 days after the termination of irradiation. High mortality at total exposures above 2000 and 1400 R given at 17 and 35 R/day, respectively, and the extremely long times required for an exposure of 4000 R at 5 R/day limited the exposure groups.

Each dog was evaluated regularly by clinical examinations, hematology and blood chemistry. All dogs becoming moribund or dying were necropsied and tissues were fixed, sectioned and examined by light and electron microscopy.

RESULTS AND DISCUSSION

A total of 354 dogs were irradiated in 13 groups. As shown in Table I, a total of 221 are still alive (January 1, 1978). There were 58 decedents during irradiation, 44 during the first 100 days following termination of irradiation, and 31 to date at times greater than 100 days following termination of irradiation.

It is apparent from the clinical, hematological and pathological data that damage to the hematopoietic system resulting in septicemia or aplastic anemia is the sole cause of death of dogs that died during irradiation, and for the first 100 days following irradiation.

Among the 31 dogs dying at times greater than 100 days after completion of irradiation, hematopoietic damage or dysfunction resulted in the death of only 10 dogs: 2 cases of anemia due to marrow aplasia; 5 cases of myeloproliferative disorders (MPD) manifested as myelogenous leukemia and monocytic leukemia; and 3 malignant lymphomas (lymphosarcomas). The nature of the hematopoietic dysfunctions was significantly altered as compared to early death, at each of the four exposure rates; there was hyperfunction (neoplasia) resulting in leukemias or related disorders in 8, and hypofunction (anemia) in only 2.

Nine nonhematopoietic malignancies also occurred among the 31 decedents. These included a carcinoma of the intestine, a squamous carcinoma of the buccal cavity, 2 angiosarcomas of the spleen, a generalized cutaneous mast cell tumor, 2 mammary carcinomas, 1 splenic neurofibrosarcoma, and 1 transitional cell tumor of the bladder.

It is premature to predict the frequency of malignancies that will occur among the remaining dogs, but the data to date can be compared to that in other irradiated and untreated dogs in our colony. A survey of tumors among untreated control and breeder animals in the colony [17] allows us to conclude that although the incidence of spontaneous tumors is high among aged control animals, the tumor types, numbers and ages at the time of death from malignancies already seen in this study are significant. The occurrence of MPD's are particularly noteworthy as none has been seen in our untreated dogs.

Among dogs irradiated at 5 and 10 R/day until death in our earlier studies, the incidence of MPD was $\sim$50% [7,9-11]. At 5 R/day, deaths from MPD ranged from 989 to 1949 days after beginning of irradiation, while at 10 R/day MPD deaths occurred between 383 and 1622 days of irradiation. In the terminated exposures being considered here, the three MPD deaths in the 10 R/day group (4000 R total exposure) were at 650 to 981 days following beginning of irradiation. The other two cases of MPD were in the groups irradiated at 5 and 17 R/day

for total exposures of 2000 R and occurred at 1358 and 729 days after beginning of irradiation, respectively. In each of the three irradiation groups where MPD has occurred, the decedents with MPD were the first to die, (with one exception) in the period more than 100 days after irradiation. All earlier deaths were acute deaths from anemia or septicemia as the result of bone marrow suppression. Similar results occurred in dogs given terminated exposures in a preliminary study in which 8 dogs received 1700 R at 17 R/day. Three died of anemia and septicemia less than 200 days after beginning of irradiation, two died of leukemia at 400-500 days and the remainder at later times of other causes [18]. MPD similarly occurred in dogs irradiated continuously until death in our previous study as a predictable sequel following a nadir and recovery of blood values [11].

It is unlikely that any more of the terminated exposure dogs will die with MPD; many have already survived longer following irradiation than those that developed MPD, and none have yet developed clinical or hematological signs of the disease.

Among dogs irradiated until death, the cases of MPD occurred as a cluster or wave of deaths as did anemias or septicemias [7,11]. When dogs were left in the irradiation field at 10 R/day until they died, MPD was the cause of death in that 50% of the group surviving longest. At 5 R/day, however, MPD occurred in the 50% dying earliest with a variety of other malignancies, degenerative and inflammatory processes occurring later [7,9]. Taken as a whole, these data on MPD, from lifetime and terminated exposures, suggest that there are relationships between dose and dose rate for induction of leukemia. It is obvious that there are responses of the marrow that are a prerequisite to leukemia [11].

Two of the three lymphomas in the present study also occurred early among the chronic survivors. One was the first chronic death in the 5 R/day, 1400 R total exposure group, and the other was the cause of death in the

fourth decedent at 10 R/day, 4000 R total exposure, following the first three deaths due to MPD. The remaining lymphoma occu-red after more than 2300 days in the 35 R/day, 1400 total dose groups.

Although the data from these terminated exposures are directed toward the study of late effects, when tabulated in conjunction with other previously published data, they allow for calculations of the LD_{50} for acute (hematopoietic depression) deaths associated with varying exposure rates. As shown in Table II, a reduction in the exposure rate increases the amount of radiation required to kill (LD_{50}), a concept that is well established but for which data at low dose rates in larger, longer-lived animals is difficult to obtain. The data presented here also show that as the exposure rate is decreased, the ability to measure or determine an LD_{50} dose becomes difficult, if not impossible. At 5 R/day (Table I) there were no acute hematopoietic deaths in any of the groups, including that given the highest total exposure of 2000 R. Similarly, even when irradiation was continued until death there were only three deaths due to hematopoietic suppression and the earliest of these was at 390 days of irradiation [7,9].It seems obvious that as the exposure rate is decreased, the percentage of dogs surviving to show late effects increases, and that below 10 R/day the most sensitive tissue or target organ shifts from the hematopoietic system to other organs or systems. This same effect is seen when the data from Table II are plotted as in Fig. 1. Here the data are plotted as the average absrobed dose, in rads, to allow comparisons to other experiments and animal species [19]. At the lowest dose rates, small changes in dose rate produce large variations in the LD_{50} dose. This is an expression of the increasing ability of the individual animal to accommodate to the irradiation damage and of variability in the site of damage, and therefore in the causes of death. Specifically, decreasing the dose rate from 26.25 to 7.5 rad/day (35 to 10 R/day) increases the LD_{50} dose from 1050 to at least 3000 rad (1400 and 4000 R, respectively) while increasing the dose

rate from 26.25 to over 750 rad/day (35 and 1000 R, respectively) only decreases the LD_{50} from 1050 to 2250 rad (1400 to 3000 R).

The hematologic response as measured by peripheral blood values is shown in Figures 2-4 where the data are plotted for dogs irradiated at 5, 10, 17 and 35 R/day to a total exposure of 1400 R. Because size appreciably influences absorbed dose [18], five male dogs 10-12,000 grams in weight that survived more than 100 days after irradiation were selected for each exposure rate group.

Although the changes in erythrocyte numbers (Fig. 2) were not as dramatic as those of the other cellular components, a depression and recovery associated with irradiation exposure and its termination was suggested even at the lowest dose rate (5 R/day). Oscillations in the values tended to obscure the responses but there are particularly clear changes in the three higher dose rates. At 35 R/day there was an abrupt depression and similarly abrupt recovery in the erythrocyte numbers over a period of approximately 50 days after termination of radiation. The apparent delay is undoubtedly related to the lag time for depression of bone marrow function to be expressed as lowered peripheral blood values, assuming an average life span of 100 days for the dog erythrocyte. Somewhat less expected was an apparent overshoot of the recovery of the erythrocyte values within 100 days after irradiation. Although pre-irradiation mean values were highest for this group, they tend to show a higher over compensation than other groups when irradiation was terminated.

The responses of the dogs in the 17 R/day group were similar to those at 35 R/day except that depressed values occurred during irradiation because of the longer time (82 days vs. 40 for 35 R/day) of irradiation, and recovery to higher than normal concentrations occurred at a slightly slower rate.

At 10 and 5 R/day the depression and recovery are less clear and the overshoot as seen at 17 and 35 R/day is equivocal without additional data and analyses.

Changes in leukocytes, as shown in Fig. 3, were much greater at the two highest exposure rates, but it is clear, even from these preliminary data, that there was a significant depression at all four exposure rates. Also, the higher the exposure rate, the more rapid the recovery following termination of irradiation. The platelet responses (Fig. 4) resembled those in the leukocytes, but, it must be remembered that the numbers plotted in the case of leukocytes represent a mixed population; granulocytes, lymphocytes and other cells. In the case of platelets, the population being monitored is homogenous and, therefore, the similarity to the leukocyte response seems even more remarkable. The similarity between the platelet and leukocyte response includes the correlation of the nadir, rate of decline and rate of recovery. The nadir reached in the case of the groups at 10 and 17 R/day, and their respective decline and recovery, are reasonable similar, but obviously different from those at 35 and 5 R/day.

The fact that the rate of recovery of platelets and leukocytes is more rapid at the higher dose rates seems somewhat paradoxical and raises a question regarding the controlling mechanisms. Possible hypotheses, which are not necessarily mutually exclusive, include the levels of poietins or circulating humoral factors related to the severity of the depression of the peripheral blood cells, and changes in the kinetics of bone marrow cell differentiation and maturation. In previous studies of the hematopoietic effects of single, brief, near-lethal doses or irradiation, and irradiation given continuously to death, these dose rate related differences were not observed. Dogs surviving brief single near-lethal doses had depression and

recovery rates related to the total dose [16]. Although the nadir and rate of depression of peripheral blood values was related to the dose rate in dogs irradiated until death (lower nadir and faster decline associated with higher dose rates), those dogs showing recovery in the face of continuing irradiation did so at essentially the same rate and independent of dose rate once the recovery pattern was established [7].

CONCLUSIONS

Although imcomplete, the interim data from this study allow tentative conclusions regarding effects of terminated exposures to continuous irradiation. A most important conclusion is that myelogenous leukemia and related disorders occur among dogs so irradiated. Although not as effective as irradiation given to death (~ 50% incidence in dogs given 5 and 10 R/day) at similar exposure rates, there have been 5 cases amont 31 dogs surviving more than 100 days after termination of irradiation. The occurrence of 3 cases of malignant lymphomas also seems highly significant.

The large number of other malignancies observed among the small number of decedents to date in the present study suggests that tumors of the soft tissues will be significantly increased compared to controls. No effect of dose or dose rate on induction of tumors other than myelogenous leukemia is apparent at this time.

Myelogenous leukemia, however, occurs at the same exposure rates as in dogs given irradiation until death and it occurs in association with recovery of the bone marrow after termination of irradiation and not at later times. This same sequence of events, marrow depression, recovery, and subsequent onset of leukemia, has been recorded by us in dogs irradiated continuously until death except that hematopoietic recovery occurs while irradiation continues [7,11].

No dog given terminated exposures at a rate of 35 R/day has developed myelogenous leukemia. Because irradiation given at 35 R/day causes severe hematopoietic depression in dogs given a total exposure of 1400 R (~ 60% die within 100 days) and rapid recovery is possible, it must be concluded that either the rate or total dose are ineffective for leukemia induction. At this time neither of the alternatives can be eliminated or proven, and it may be that both are correct.

Based on preliminary analysis of the response of the peripheral blood values, there is a direct correlation, not unexpected, between the rate and depth of depression of these values and the exposure rate when similar total exposures are given. Unexpected, however, is the more rapid recovery of these values, after irradiation termination, in the dogs in the higher exposure groups. This inverse relationship between rate of recovery and exposure rate requires additional analyses for confirmation and explanation.

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FIGURE LEGENDS

FIG. 1. LD_{50} dose for dogs given whole-body gamma irradiation at various dose rates. Sources of the data are given in Table II.

FIG. 2. Erythrocyte values in dogs given 1400 R whole-body gamma irradiation at four exposure rates. Each point is the mean value derived from five dogs.

FIG. 3. Total leukocyte values in dogs given 1400 R whole-body gamma irradiation at four exposure rates. Each point is the mean value derived from five dogs.

FIG. 4. Platelet values in dogs given 1400 R whole-body gamma irradiation at four exposure rates. Each point is the mean value derived from five dogs.

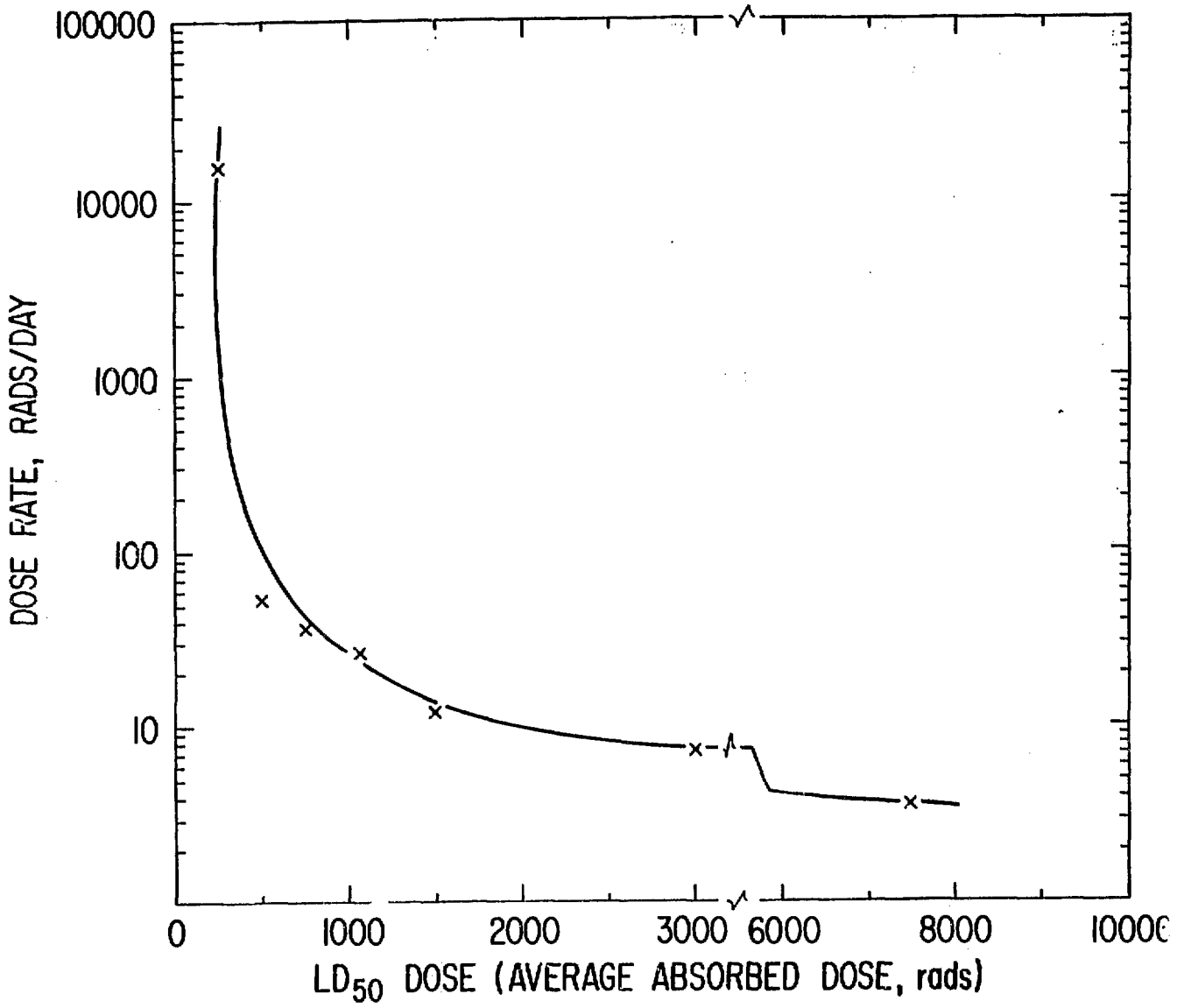

FIG. 1 LD_{50} dose for dogs given whole-body gamma irradiation at various dose rates. Sources of the data are given in Table II.

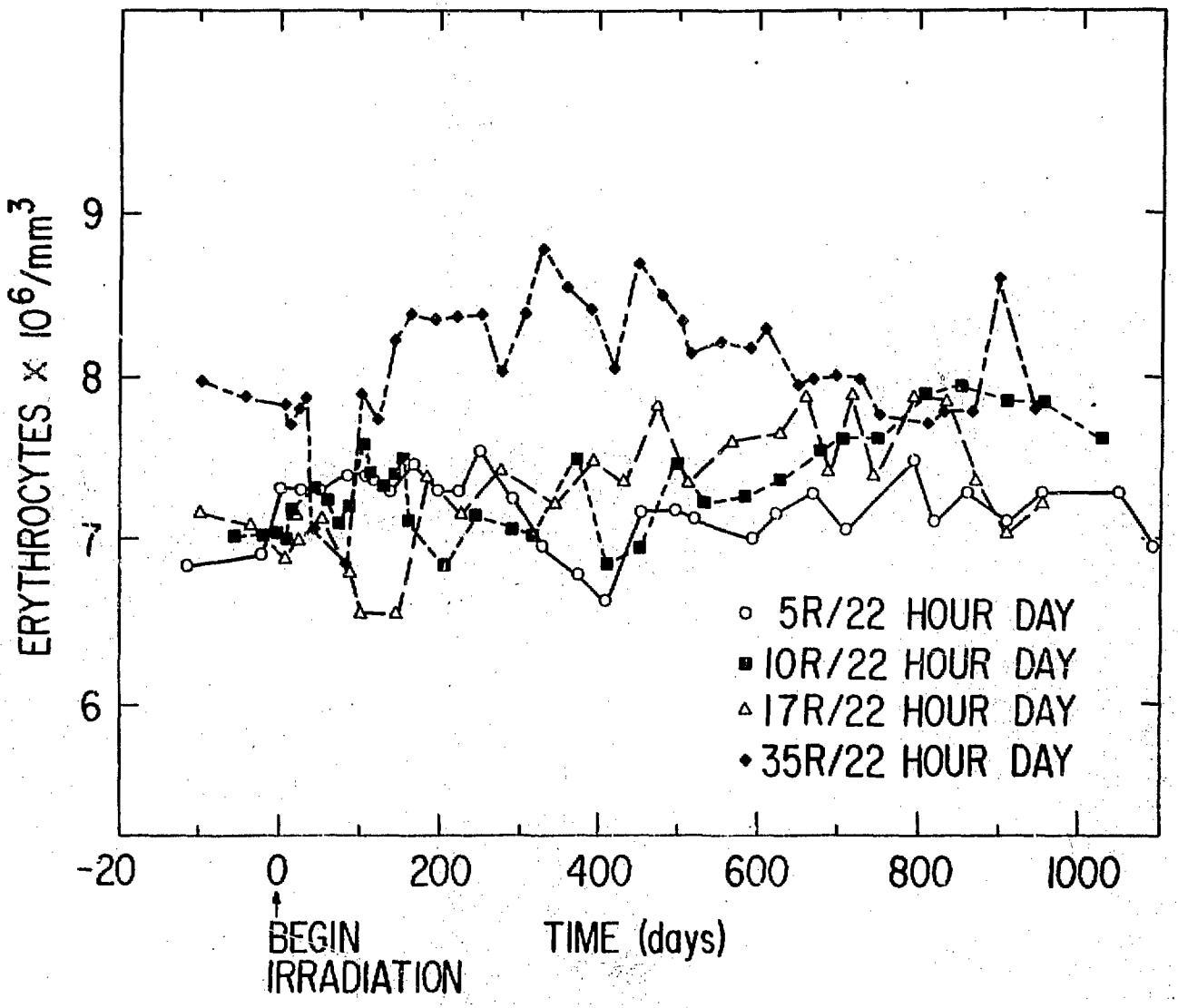

FIG. 2 Erythrocyte values in dogs given 1400 R whole-body irradiation at four exposure rates. Each point is the mean value derived from five dogs.

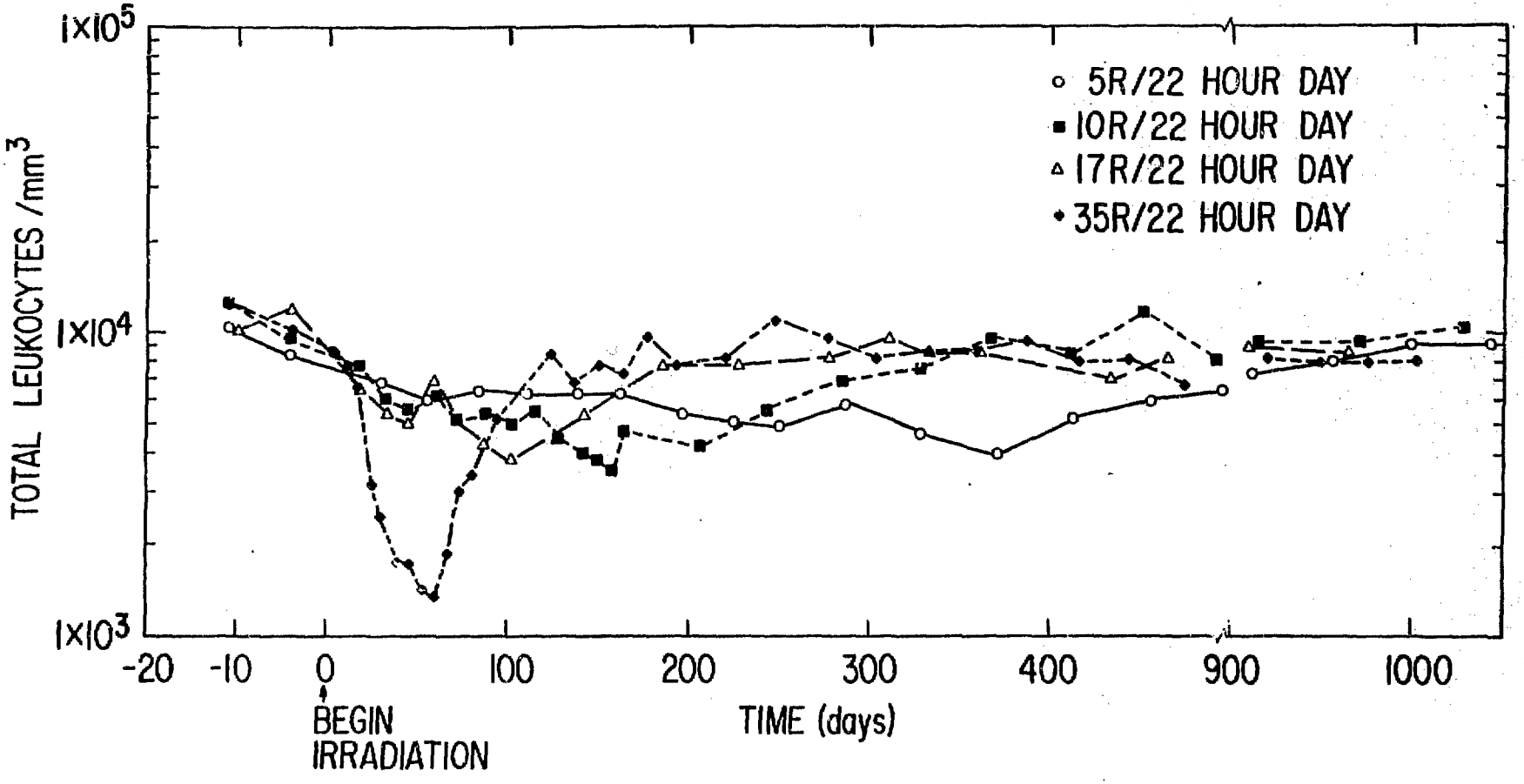

FIG. 3 Total leukocyte values in dogs given 1400 R whole-body gamma irradiation at four exposure rates. Each point is the mean value derived from five dogs.

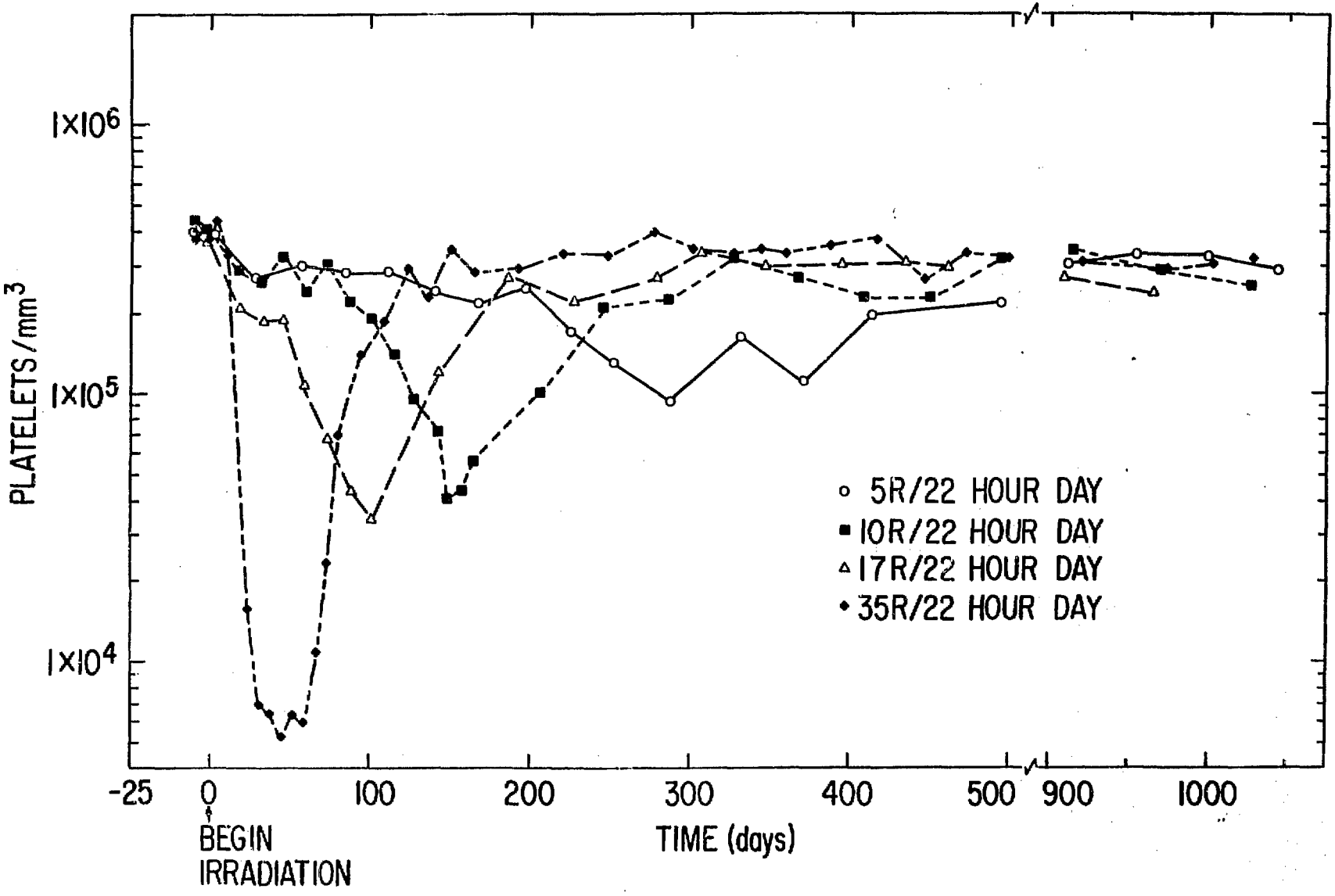

FIG. 4 Platelet values in dogs given 1400 R whole-body gamma irradiation at four exposure rates. Each point is the mean value derived from five dogs.

TABLE I

Exp. Rate	Total Exp.	Total Dogs	Number Dead and Cause[b]				Number Alive and Age (in days)[a]	
			During Irradiation	After Irradiation < 100 days	After Irradiation > 100 days	No. days[a]		
5 R	600 R	20	0	0	0		20	438-489
	1400 R	24	0	0	1-lymphosarcoma	(931)	23	1400-2106
	2000 R	20	0	0	1-MPD	(729)	19	993-1393
10 R	600 R	20	0	0	0		20	309-663
	1400 R	24	2-S	2-A	1-paresis & hydrocephalis		18	1233-1380
					1-heartworms			
	2000 R	28	2-A	1-S	1-anemia		16	1653-1898
				6-A	1-pneumonia			
					1-epilepsy			
	4000 R	31	1-S	3-A	3-MPD	(655,812,981)	8	2101-2794
			8-A		1-lymphosarcoma	(1016)		
					2-pneumonia			
					1-intestinal carcinoma	(2375)		
					1-anemia & mammary carcinoma			
					1-squamous carcinoma & angiosarcoma	(2468)		
					1-endometritis & mammary carcinoma	(2479)		
					1-trauma			
17 R	600 R	20	0	0	0		20	257-660
	1400 R	25	0	3-A	0		22	884-1066
	2000 R	53	17-S	6-A	1-anemia		18	102-1843
			3-A	6-S	1-monocytic leukemia	(1358)		
				1-H				
	4000 R	24	6-A	1-A	2-pneumonia		8	2347-2893
			7-S					
35 R	600 R	20	0	0	0		20	262-438
	1400 R	45	12-S	15-S	3-endometritis (& 1 bladder tumor)	(2889)	9	2893-3411
					1-enteritis			
					1-splenic hematoma			
					1-lymphosarcoma	(2381)		
					1-neurofibrosarcoma	(2516)		
					1-mast cell tumor	(2899)		
					1-angiosarcoma	(775)		
		354	58	44	31		221	

[a]No. days since beginning of irradiation. Because dogs were not all irradiated at one time the time of survival varies within each group.

[b]S = septicemia; A = anemia, MPD = myeloproliferative disorder; H = hemorrhage.

TABLE II

Effect of Exposure Rate of Terminated Exposures of ^{60}Co γ-rays on Survival of Beagles

Exposure Rate (Roentgens)		LD_{50} Estimate for Hematopoietic Suppression Average Absorbed Dose, rads)	Reference
15 R/minute (21,600 R/day)	=	258 (mean time of death = ∿ 20 days)	16
.050 R/minute (72 R/day)	=	∿ 500 (4/4 @ 594 rads in 22 days)	7
.0347 R/minute (50 R/day)	=	∿ 750 (0/4 @ 412 rads)	7
.0243 R/minute (35 R/day)	=	∿ 1050 (27/45 @ 1050 rads in mean of 41.8 days)	Table I
0170 R/minute (24.5 R/day)	=	∿ 1950 (3/8 @ 1837 rads in mean of 113 days)	18
.0118 R/minute (17 R/day)	=	∿ 1500 (33/53 @ 1500 rads in mean of 121.8 days)	Table I
.0069 R/minute (10 R/day)	=	2250-3000 (9/28 @ 1500 rads in mean of 214 days) (12/31 @ 3000 rads in mean of 291.6 days)	Table I
.0034 R/minute (5 R/day)	=	? (2/24 in 437 days if radaition is continuous)	7